Medical Staff Conference

Management of Hypercholesterolemia
A Primary Care Perspective

Discussant
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These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *The therapy for hypercholesterolemia and other hyperlipidemias is a major problem now facing the primary care physician and anyone else who is concerned about the treatment of impending or real vascular disease. We are fortunate to have Dr Robert Baron at this conference to discuss the subject of the management of hypercholesterolemia from the primary care perspective.*

ROBERT B. BARON, MD, MS†: The focus of this review will be recent developments and persistent controversies concerning the relationship of hypercholesterolemia to coronary artery disease and the development of a practical approach to patient management in primary care practice. Specifically, I will address five questions:

- Why treat hypercholesterolemia?
- Who should be screened?
- Who should be treated?
- Is diet therapy effective? and
- Have the magic bullets finally arrived for drug therapy?

Why Treat Hypercholesterolemia?

Our current belief that increased blood cholesterol levels, particularly increased low-density lipoprotein (LDL)-cholesterol levels, are strongly and causally related to coronary artery disease comes from the results of many epidemiologic studies. Clinical experience with patients with genetic hyperlipoproteinemia and laboratory evidence from various disciplines have further strengthened this belief. Yet, only in the past year, with the publication of the report of the National Cholesterol Education Program (NCEP) of the National Heart, Lung, and Blood Institute,[1] has an aggressive approach to detecting and treating hypercholesterolemia been strongly advocated. Five recent studies have provided sufficient additional evidence to justify such an approach.

The long-term follow-up study of 361,622 men screened for the Multiple Risk Factor Intervention Trial (MRFIT)[2] has greatly clarified the relationship between blood cholesterol levels and coronary artery disease. In this large cohort of middle-aged men, the average blood cholesterol value was about 5.2 mmol per liter (200 mg per dl). Cholesterol levels of 6.4 mmol per liter (245 mg per dl) were associated with a twofold greater risk of dying of coronary artery disease in six years. Cholesterol levels of 7.8 mmol per liter (300 mg per dl) doubled the risk again. Lower than average cholesterol levels were associated with a decreased risk. An even more striking observation from this study was the realization that the relationships between cholesterol, coronary artery disease mortality, and total mortality were virtually identical to the relationships between hypertension and the same clinical end points. This observation has strongly suggested that both our clinical and public health approaches to the management of these two risk factors should be similar.

The Lipid Research Clinic Coronary Primary Prevention Trial[3,4] was a randomized study of 3,806 men, aged 35 to 59 years, with total cholesterol levels of greater than 6.9 mmol per liter (265 mg per dl). Subjects were randomly assigned to receive a diet plus placebo or a diet plus cholestyramine and were observed for seven to ten years. Administering cholestyramine resulted in a 13% reduction in total cholesterol levels, a 20% reduction in LDL-cholesterol levels, and a 3% increase in high-density lipoprotein (HDL)-cholesterol levels. The number of definite coronary deaths decreased 21%, and all coronary end points decreased 17%. Total mortality rates were not reduced in the experimental group, however, due to an increase in noncardiovascular mortality rates, including suicides and accidents. This was the first large multicenter study to show a clear reduction in coronary artery disease mortality with lipid modification.

The Helsinki Heart Study was a randomized, double-blind, five-year comparison of the use of gemfibrizol and placebo in 4,081 men aged 40 to 55 years with non-HDL-cholesterol levels of more than 5.2 mmol per liter.[5] Using gemfibrizol caused an 8% reduction in total cholesterol levels, an 8% reduction in LDL-cholesterol values, a 35% reduction in triglyceride levels, and a 10% increase in HDL-cholesterol levels. A 34% decrease in the incidence of cardiac events was seen in the gemfibrizol-treated group. Although a 26% decrease in coronary artery disease mortality was also seen, this was not statistically significant. There was

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
LDL = low-density lipoprotein
NCEP = National Cholesterol Education Program

also no difference in total mortality. Analysis of the effects of the lipid alterations on coronary artery disease suggested that the changes in LDL- and HDL-cholesterol levels were strongly associated with the decline in the incidence of coronary artery disease while the reduction of triglyceride levels was not.[6] This was the first major clinical trial to show that raising the HDL-cholesterol levels results in a reduction in the coronary disease incidence.

The Cholesterol-Lowering Atherosclerosis Study randomly assigned 162 nonsmoking men aged 40 to 50 years with previous coronary artery bypass grafts to receive either diet therapy and placebo or a combined regimen of diet, colestipol hydrochloride, and nicotinic acid.[7] The combined treatment resulted in a 26% reduction in total cholesterol values, a 43% reduction in LDL-cholesterol levels, and a 37% increase in HDL-cholesterol levels. A blind assessment of angiograms showed a regression of atherosclerotic lesions in 16.2% of drug-treated subjects and 2.4% of placebo-treated subjects and fewer new lesions in both native vessels and grafts in drug-treated subjects. This was the first major clinical trial to show that aggressively reducing LDL-cholesterol levels can result in a regression of coronary atherosclerosis in some patients.

The Coronary Drug Project was a randomized trial conducted between 1966 and 1975 of 8,341 men aged 30 to 64 years with an electrocardiographically documented myocardial infarction at least three months before entry.[8] Subjects were randomly assigned to receive one of six regimens including low-dose estrogen, high-dose estrogen, dextrothyroxine sodium, clofibrate, nicotinic acid, and placebo. The initial three regimens were discontinued early in the study because of adverse events. At the end of the study, no efficacy was found for the use of clofibrate whereas nicotinic acid treatment showed a modest decrease in the incidence of nonfatal myocardial infarctions. No effect on total mortality was observed. Using nicotinic acid resulted in a 10% decrease in total cholesterol levels and a 26% decrease in triglycerides. A long-term follow-up of 6,000 men in 1984 showed that patients treated with nicotinic acid during the trial had an 11% decrease in subsequent total mortality rates.[9] This was the first major clinical trial to show that modifying blood lipids can result in a decrease in total mortality.

Despite this evidence, some authorities have questioned the cost-effectiveness of an aggressive cholesterol-lowering treatment program that requires frequent physician and dietician visits, medications, and laboratory tests.[10] A recent comparison of alternative strategies for managing coronary risk has clearly shown that a smoking-cessation program or even surgical treatment of left main coronary artery disease is more cost-effective than cholesterol-lowering treatments.[11] Determining the cost per year of life saved by reducing cholesterol levels largely depends on the medication chosen. Less expensive medications such as nicotinic acid or oat bran make cholesterol reduction more cost-effective than the treatment of moderate hypertension, whereas the use of expensive medications such as colestipol in individual packets is four times more expensive. These are difficult social issues that must be resolved on a societal level in the context of other health- and non-health-related costs.

Despite these controversies, the National Cholesterol Education Program has recently embarked on a nationwide effort to improve the detection, evaluation, and treatment of hypercholesterolemia in adults. The following remarks are largely based on the NCEP perspective.

Whom to Screen? Initial Classification by Total Cholesterol Levels

Each adult patient should have a total blood cholesterol level measured at least once every five years. Fasting before the specimen is drawn is not required. Despite the simplicity of this recommendation, the results of a recent survey by the Centers for Disease Control suggest that we still have a long way to go to meet this goal.[12] Only 47% of persons surveyed have ever had a blood cholesterol level measured, only 19% have ever been told their cholesterol level, and only 6% actually know their blood cholesterol level. Blood cholesterol levels can then be categorized as desirable (less than 5.20 mmol per liter [200 mg per dl]), borderline high (5.20 to 6.21 mmol per liter [200 to 239 mg per dl]), or high (6.24 mmol per liter [240 mg per dl] or higher). By dividing a continuous biologic variable into discrete categories, we are, by definition, creating arbitrary classifications. These levels have been chosen primarily because 6.24 mmol per liter is the 75th percentile of cholesterol levels in the United States and is the level at which the risk of dying of coronary artery disease doubles.

The initial follow-up is based on this categorization. Patients with desirable blood cholesterol levels can be reassured and advised to have their cholesterol levels rechecked in five years. It is important that such patients not become overly focused on their blood cholesterol, particularly at the expense of other preventive health measures. Patients with higher blood cholesterol levels need further management, as will be discussed.

The next step of classifying patients with borderline cholesterol levels is determined by the presence or absence of coronary artery disease or its risk factors. The other risk factors to consider are shown in Table 1. Male sex is considered a risk factor because of the higher incidence of coronary disease found in men at any given cholesterol level. A family history of premature heart disease is defined as a myocardial infarction or sudden death in a parent or sibling before age 55. Hypertension and diabetes mellitus are risk factors whether or not they are being treated. Smoking more than ten cigarettes per day, a history of stroke or peripheral vascular disease, obesity of greater than 30% overweight, and an

TABLE 1.—*Risk Factors for Coronary Artery Disease (CAD) Other Than Borderline Cholesterol Levels*

Male sex
Family history of premature CAD (definite MI or sudden death before age 55 in a parent or sibling)
Cigarette smoking (more than 10 cigarettes per day)
Hypertension
Low HDL-cholesterol (<0.9 mmol per liter [35 mg per dl])
Diabetes mellitus
History of definite cerebrovascular or occlusive peripheral vascular disease
Obesity (>30% over "desirable weight")

HDL=high-density lipoprotein, MI=myocardial infarction

HDL-cholesterol level of less than 0.91 mmol per liter (35 mg per dl) are also independent risk factors.

Although the multiplicative relationship between risk factors has been known for some time, this is the first time that a national policy recommendation for the management of one risk factor is affected by the presence of other risk factors. Patients with borderline cholesterol levels who do not have two or more risk factors are given dietary information and rechecked annually to screen for a further elevation of cholesterol levels, but an intensive intervention is not needed. Patients with borderline cholesterol levels who already have coronary artery disease or who have two or more other coronary risk factors require the determination of an LDL-cholesterol level, as will be described.

This emphasis on associated risk factors is based on the principle that the greater a persons's risk of having the disease being prevented, the greater the possible benefit from a preventive intervention. Table 2 shows a comparison of the risk of death from coronary artery disease per 1,000 men based on blood cholesterol values in two groups of men: hypertensive smokers and normotensive nonsmokers. Although the relative risk of coronary disease as a function of cholesterol elevation is approximately equivalent (6.4/1.6 versus 21.4/6.3), the absolute number of preventable deaths is greater in the high-risk group (15.1 versus 4.8).

Whom to Treat? Classification by LDL-Cholesterol Levels

All patients with high blood cholesterol levels (>6.24 mmol per liter) and those patients with borderline blood cholesterol levels (5.20 to 6.21 mmol per liter) who have either coronary artery disease or two or more other risk factors should be further evaluated by the determination of an LDL-cholesterol level. The LDL-cholesterol value is estimated from fasting measurements of serum lipids using the following equation: LDL-cholesterol = total cholesterol − (HDL-cholesterol) − (triglycerides/5). At least two LDL-cholesterol estimations should be done and averaged. Despite improved standardization of most large laboratories in the past year, there remain a 2% to 3% analytic variability and a 10% intraindividual biologic variability in cholesterol measurements.

Patients are then further categorized based on the LDL-cholesterol levels. Values of less than 3.38 mmol per liter (130 mg per dl) are desirable, and no further treatment is indicated. Those between 3.38 and 4.13 mmol per liter (130 and 159 mg per dl) are borderline; levels above 4.16 mmol per liter (160 mg per dl) are high. Patients with borderline or high LDL-cholesterol levels should be evaluated with a careful history and physical examination to rule out secondary causes of hypercholesterolemia and should be assessed for a genetic hyperlipidemia. The treatment of borderline and high LDL-cholesterol levels should then be initiated according to the guidelines shown in Table 3.

TABLE 2.—*Coronary Artery Disease Deaths Per 1,000 in Men Aged 35 to 37 Years With an Average Follow-up of 6 Years According to Serum Cholesterol Quintile and Presence or Absence of Other Risk Factors**

Serum Cholesterol Quintile, mmol/liter (mg/dl)	Normotensive Nonsmoker	Hypertensive Smoker
<4.73 (182)	1.6	6.3
4.73-5.25 (182-202)	2.5	10.3
5.28-5.72 (203-220)	2.7	15.5
5.75-6.34 (221-244)	3.8	16.6
>6.37 (245)	6.4	21.4

*From Martin et al.[2]

TABLE 3.—*Indications for Treatment Based on LDL-Cholesterol Levels*

Dietary Treatment	LDL-Cholesterol Level: Initiation Level, mmol/liter (mg/dl)	LDL-Cholesterol Level: Minimal Goal, mmol/liter (mg/dl)
Without CAD or 2 other risk factors	≥4.16 (160)	<4.16 (160)
With CAD or 2 other risk factors	≥3.38 (130)	<3.38 (130)
Drug Treatment		
Without CAD or 2 other risk factors	≥4.94 (190)	<4.16 (160)
With CAD or 2 other risk factors	≥4.16 (160)	<3.38 (130)

CAD=coronary artery disease, LDL=low-density lipoprotein

Dietary Treatment—Can It Be Done?

Only three dietary factors raise blood cholesterol levels: saturated fatty acids, dietary cholesterol, and excess calories resulting in obesity. The goal of the dietary treatment of hypercholesterolemia is to reduce the intake of these three dietary factors.

Unfortunately, dietary changes are difficult for many patients. Large clinical trials of dietary changes have generally resulted in relatively small average changes in dietary cholesterol, about 5% to 10%. Moreover, physicians commonly have little experience in promoting dietary changes, and most physicians' attempts at the dietary treatment of hypercholesterolemia are only cursory. With the appropriate guidance, however, many patients are able to change their diets substantially, obviating the need for drug treatment. Reductions in blood cholesterol levels of greater than 20% can, at times, be achieved.

Successful dietary change requires that patients be motivated to initiate new action and that they have information about the need to change their diets, specific skills to carry out new patterns of behavior, and a supportive environment in which to carry out change. Most physicians are comfortable with providing information to patients and providing support. More emphasis must be placed on assessing and enhancing motivation and on developing specific skills.

Motivation can be assessed by standard interviewing techniques, by assigning specific tasks such as a three-day diet record, and by scheduling a separate appointment to initiate diet therapy. Only motivated patients should be begun on intensive dietary therapy. Gentle attempts to enhance motivation by providing additional information, skills, and support should be continued, and such patients should be seen for regular follow-up visits to reassess motivation.

The development of specific skills for behavior change is more in the realm of behaviorists than of physicians; nonetheless, a number of simple skills can be taught by physicians to facilitate behavior change.[13] Specific goals can be negotiated between patient and physician. These should be tailored to the patient and should be measurable, achievable, recorded in the patient's record, and rewarded. Monitoring of behaviors, particularly food intake, allows patients to correlate specific behaviors with specific outcomes. Patients can

be taught to identify and avoid situations that impede the desired changes. Rehearsal or role-playing can be used to prepare for difficult unavoidable situations, and planning facilitates appropriate shopping and food preparation.

Making changes in small incremental steps allows the building of new experiences without taking excessive risks, and early successes are reinforced. Small failures are less damaging than large ones and can be used as effective teaching tools. Specific feedback by a review of diet records, the patient's report, and measured blood cholesterol levels provides the patient with support and further helps to build skills. Finally, patients can be taught that they are not expected to follow the diet 100% of the time. Even 90% compliance allows patients to have two meals per week with liberalized food choices without having a significant effect on their blood cholesterol levels.

Throughout this process the physician must maintain a positive attitude toward diet modification. Personal attempts by physicians at similar dietary changes will add considerable insight into this process.

Recommended Diets

The National Cholesterol Education Program recommends diet modification in two steps. The macronutrient composition of each is shown in Table 4.

The first goal of the diet is to reduce the total dietary fat to less than 30% of total calories. This has two purposes: to reduce the amount of saturated fat and to reduce the total calorie intake. The fat content of current US diets averages 35% to 40% of calories. Previous recommendations have been that patients who fail a step-one diet reduce their total fat consumption to less than 20% of their total calories. Recent evidence suggests that this is not necessary if saturated fat intake is further reduced.[14,15] Overweight patients, however, may need to reduce their total dietary fat to less than 20% to facilitate weight loss.

Reducing the intake of saturated fat is the single most important element of the dietary treatment of hypercholesterolemia. Current US diets contain an average of 13% to 17% of total calories as saturated fat. In the step-one diet, saturated fat should be decreased to less than 10%. This decrease in saturated fatty acid intake simultaneously results in the recommended decrease in total fat. A further reduction to less than 7% is recommended in the step-two diet. Saturated fats are primarily found in butterfat, beef and pork fat, and three plant oils—palm, palm kernel, and coconut—commonly used in commercial baked goods. More than 60% of the saturated fat in the US diet is contained in ten types of foods (Table 5).[16]

Results of a recent study suggest that the saturated fatty acids do not have equivalent effects on blood lipids.[17] Using liquid formula diets, Bonanome and Grundy compared diets with equal amounts of the saturated fatty acids palmitic (16:0) and stearic (18:0) and the monounsaturated fatty acid, oleic (18:1). Compared with the palmitic acid diet, the intake of both stearic and oleic acids resulted in a reduction in blood cholesterol values. Although stearic acid is an important fat in beef and chocolate, these foods also contain substantial amounts of palmitic acid and dietary cholesterol, and their intake should be restricted on a cholesterol-lowering diet. Polyunsaturated fats can be used to partially replace saturated fat in the diet. A one-for-one replacement of saturated fatty acids by polyunsaturated fatty acids results in a decrease in blood cholesterol levels. The current US intake is 7% of calories; the recommended intake is 10%. For patients attempting to lose weight, maintaining the 7% figure is preferable. Levels above 10% are no longer recommended owing to the lack of information concerning the long-term safety of such high intakes. Polyunsaturated fatty acids also lower HDL-cholesterol levels more than equal amounts of monounsaturated fatty acids.[18] Polyunsaturated fatty acids are found in several vegetable oils including safflower, sunflower, soybean, and corn.

Omega (ω)-3 fatty acids are also polyunsaturated fatty acids. These fatty acids have been shown to decrease blood triglyceride levels in high doses but have a variable effect on LDL- and HDL-cholesterol levels.[19,20] The major source of ω-3 fatty acids is fish oil. Consuming ω-3 fatty acids is not equivalent to consuming fish. Some fish, such as mackerel and salmon, contain relatively large amounts of ω-3 acids while others, such as swordfish, do not. Epidemiologic evidence suggests that eating fish, independent of the ω-3 fatty acid content, is associated with a decreased risk of coronary artery disease.[21] In any case, fish is an excellent dietary substitute for meat.

Until recently, monounsaturated fats were thought to have a neutral effect on blood cholesterol. Recent evidence suggests, however, that monounsaturated fatty acids are equivalent to polyunsaturated fats in lowering LDL-cholesterol levels when either is substituted for saturated fatty acids and do not show the HDL-cholesterol-lowering effect seen with polyunsaturated fatty acids.[18,22] The current US diet contains 14% to 16% of calories as monounsaturated fats,

TABLE 4.—*Macronutrient Composition of Step-One and Step-Two Diets*

Nutrient	Recommended Intake, % of Total Calories	
	Step-One Diet	Step-Two Diet
Total fat	<30	
Saturated fat	<10	<7
Polyunsaturated fat	Up to 10	
Monounsaturated fat	10-15	
Carbohydrates	50-60	
Protein	10-20	
Cholesterol	<300*	<200*
Total calories	To achieve desirable weight	

*Milligrams per day.

TABLE 5.—*Major Contributors of Saturated Fatty Acids in the American Diet**

Rank	Food	Dietary Saturated Fatty Acid, % of Calories
1	Hamburgers, cheeseburgers, meat loaf	9.3
2	Whole milk, whole milk beverages	9.1
3	Cheeses, excluding cottage cheese	7.3
4	Beef steaks, roasts	7.3
5	Hot dogs, ham, luncheon meats	7.0
6	Doughnuts, cookies, cake	4.8
7	Eggs	4.5
8	Pork, including chops, roasts	4.0
9	Butter	3.7
10	White bread, rolls, crackers	3.2
	Total	60.2

*From Block et al.[16]

mostly from animal fats. When the amount of dietary fat is decreased, a larger portion of monounsaturated fats will come from vegetable oils. Canola oil and olive oil are two vegetable oils that are high in monounsaturated fats and low in saturated fats.

Dietary cholesterol has a less important effect on blood cholesterol levels than dietary fat. Although increases in dietary cholesterol typically raise the blood cholesterol level, the increase is rarely striking and varies from person to person. An additional concern, however, is that dietary cholesterol is absorbed as chylomicrons that are degraded into cholesterol-rich chylomicron remnants, which themselves may be atherogenic. Dietary cholesterol is found in animal products including egg yolks, organ meats, some shellfish, butterfat, and animal flesh (including chicken and fish). Ten types of foods contribute more than 77% of the dietary cholesterol in the US diet (Table 6).[16] Interestingly, the list is similar to the saturated fat list.

In patients who are overweight, total calories should be reduced to attain a normal body weight. For many patients this is the most difficult part of a cholesterol-lowering diet. Calorie reduction and weight loss will often, but not always, decrease LDL-cholesterol levels. Blood triglyceride levels, however, virtually always decrease, and HDL-cholesterol levels commonly rise.

Changes in dietary fiber intake can also result in cholesterol lowering. Dietary fiber is either insoluble or soluble. Insoluble fiber adds bulk to the stool but has no significant effect on blood cholesterol levels. High intakes of soluble fiber—15 to 25 grams a day—however, have been shown to decrease blood cholesterol levels by 10% to 20%.[23,24] Soluble fibers include pectins, certain gums, and psyllium. A common source of one of the cholesterol-lowering gums, β-glucan, is found in oats and beans.

Alcohol has no direct effect on LDL-cholesterol levels but does increase both triglyceride and HDL-cholesterol levels.[25] It is not clear if the associated rise in HDL-cholesterol offers protection against coronary artery disease. Patients who consume moderate amounts of alcohol—less than 2 ounces a day—can continue to do so; patients who do not drink should not be encouraged to do so.

Aerobic exercise facilitates weight loss and has a direct effect on serum lipids, lowering LDL-cholesterol and triglyceride values, and increasing HDL-cholesterol levels. Recent evidence suggests that a well-designed exercise program is as effective as diet in improving the blood lipid profile.[26] Patients should be encouraged to exercise aerobically for 20 to 30 minutes four to five times per week. A heart rate of 70% to 80% of maximum predicted heart rate should be achieved and sustained during exercise.

TABLE 6.—*Major Contributors of Dietary Cholesterol in the American Diet**

Rank	Food	Dietary Cholesterol, %	mg/d
1	Egg yolks	35.9	162
2	Beef steaks, roasts	8.7	39
3	Hamburgers, cheeseburgers, meat loaf	7.3	33
4	Whole milk, whole milk beverages	5.4	24
5	Hot dogs, ham, luncheon meats	4.3	20
6	Pork, including chops, roasts	3.6	16
7	Doughnuts, cookies, cake	3.6	16
8	Cheeses, excluding cottage cheese	3.1	14
9	Liver	2.7	12
10	Chicken and turkey, excluding fried	2.6	12
	Total	77.2	348

*From Block et al.[16]

Practical Aspects in Designing Diets

In practical terms, most patients and physicians are unable to differentiate between the step-one and step-two diets. An alternative is to begin with a qualitative approach, followed by a quantitative approach.

The qualitative approach divides foods into those that should be chosen and those that should be decreased. A wide variety of excellent patient education materials are available to facilitate this process. Food lists can then be tailored to patients' individual eating habits and food preferences. This approach should be followed for at least three months with visits and blood cholesterol determinations one and three months after the diet's initiation.

Further reducing the saturated fat intake to less than 7% of total calories and dietary cholesterol to 200 mg per day requires a more quantitative approach.[27] By estimating patients' daily energy requirements and calculating the daily intake of saturated fat, highly motivated patients can be instructed to keep daily food records tracking their saturated fat intake. Although a number of patient-oriented books and manuals are available to assist patients with this process, a referral to a registered dietician is often necessary to adequately teach the step-two diet. As with the step-one diet, patients should be seen one and three months after initiation.

Drug Therapy—Have the Magic Bullets Arrived?

Patients with elevated LDL-cholesterol levels for whom six months of intensive dietary therapy fails should be considered for drug treatment. The decision to initiate drug therapy must be made after careful deliberation and discussion with the patient. Throughout the process of managing hypercholesterolemia, but particularly when initiating drug therapy, the physician and the patient should realize that they are treating a risk factor, not a disease. Although many patients will choose to do everything possible to decrease their risk of coronary artery disease, other patients may prefer to take the risk and avoid drug therapy.

The principles of successful drug treatment of hypercholesterolemia are analogous to drug treatment of hypertension. Patients should be clear about the goals of therapy and the need for long-term treatment. Careful attention must be paid to common side effects and their prevention. Every drug, but particularly the bile acid-binding resins and nicotinic acid, should be begun at low dosages. Once- or twice-a-day dosing is preferred whenever possible. Frequent follow-up and monitoring are necessary to prevent complications and maximize compliance. The need for concurrent diet therapy should be emphasized. Periodic trials of decreasing drug doses or discontinuing the use of the medications in well-controlled patients should be considered.

The major drugs for consideration by primary care providers are the bile acid-binding resins, cholestyramine resin and colestipol; the B-complex vitamin, nicotinic acid; the fibric acid derivative, gemfibrizol; and the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, lovastatin. A number of other agents are under active investigation, particularly other fibric acid derivatives and HMG-CoA reductase inhibitors, and may soon be available.

TABLE 7.—*Lipid-Modifying Effects of Major Cholesterol-Lowering Medications*

Drug	Lipids, % Δ		
	LDL-Cholesterol	HDL-Cholesterol	Triglycerides
Nicotinic acid	−15-20	+30-35	−25-30
Resins	−15-25	+5	+10
Gemfibrizol	−15	+15-20	−35-50
Lovastatin	−20-45	+10	−20

HDL = high-density lipoprotein, LDL = low-density lipoprotein

In selecting drugs from the current list of available drugs, at least five factors should be considered. These are their lipid-modifying effects, proven efficacy, long-term safety, convenience and side effects, and cost. Each of the four classes of medications have advantages and disadvantages in these regards. The choice of one drug over another will reflect both physician biases about drug use and patient preferences. Although the lipid-modifying effects of each of the drugs are excellent, they are not all equivalent (Table 7). Nicotinic acid, the bile acid-binding resins, and gemfibrizol have approximately equivalent LDL-cholesterol-lowering effects while lovastatin is about twice as effective. Changes in HDL-cholesterol levels are more diverse. The use of nicotinic acid and gemfibrizol results in excellent increases in HDL-cholesterol, lovastatin has an intermediate effect, and the resins a modest effect. Changes in triglyceride levels are even more varied. Nicotinic acid, gemfibrizol, and lovastatin all have significant triglyceride-lowering effects, whereas the resins elevate triglyceride levels. Although changes in triglyceride levels appear to have little effect on coronary artery disease, the triglyceride-raising effect of the resins may be important in patients with pronounced hypertriglyceridemia (>54.5 mmol per liter [500 mg per dl]) due to the risk of provoking pancreatitis.

The long-term efficacy and safety of these drugs has been investigated in the large clinical trials discussed earlier. Only nicotinic acid has to date been shown to reduce total mortality. Nicotinic acid, cholestyramine, and gemfibrizol reduce coronary disease end points. All three drugs have been shown to be safe in trials of five to seven years. Although lovastatin has not yet been studied in a large clinical trial, most authorities are confident that its use will be extremely effective in reducing the incidence of coronary artery disease. The unresolved concern is, of course, its long-term safety. Only about 1,000 patients have been carefully observed for at least a year while taking lovastatin. A quarter of these have been observed for up to four years. These are insufficient numbers to detect a relatively rare but life-threatening complication of the drug. Since its public release, however, hundreds of thousands of patients have been treated with lovastatin. Any serious side effects should be seen in the near future. My practice is to reserve lovastatin therapy for patients with genetic hyperlipoproteinemia and substantially elevated blood cholesterol levels, refractory patients, and patients in whom compliance and convenience are paramount.

Differences in medication cost are also noteworthy. Surprisingly, there are minimal differences in the wholesale cost among these drugs when equipotent doses are compared.[28] The only major exception is generic nicotinic acid, which is approximately a sixth the cost of the other medications.

In practical terms, differences in side effects and convenience and their influence on compliance often determine the choice of medication in a given patient. Although nicotinic acid offers a number of advantages as noted above, it can be a difficult drug to use for many patients. The major obstacle to its use is the severe flushing experienced by most patients. The flushing is prostaglandin mediated and can often be inhibited by taking one aspirin 30 minutes before each dose of niacin. Sustained-action nicotinic acid preparations are nearly as effective at modifying lipids, usually cause less flushing, but are more expensive. Other common side effects of nicotinic acid include gastrointestinal distress, hepatic toxicity, glucose intolerance, hyperuricemia, and dry eyes. Nicotinic acid should be used with caution in patients with diabetes mellitus, and its use should be avoided in patients with active gout, liver disease, or peptic ulcer disease.

To minimize side effects and maximize long-term patient acceptance, nicotinic acid therapy should be begun at low doses—usually 100 mg with the evening meal. The dosage can be increased every four to seven days until a dosage of 1.5 to 2.0 grams per day is reached. If the goal LDL-cholesterol level has not been reached, the dosage can be increased to 3 to 6 grams in two or three doses per day.

The most frequent side effects of the bile acid-binding resins cholestyramine and colestipol are gastrointestinal. Constipation, abdominal pain, heartburn, nausea, belching, and bloating are common, and patients often complain of the medications' gritty taste and a dry mouth. Side effects may be avoided by taking the resins with fruit juice instead of water, increasing the intake of fluid and dietary fiber to prevent constipation, and taking them with meals. Stool softeners may occasionally be useful. A recently marketed confectionery form of cholestyramine may be preferable for some patients, but it is expensive and high in calories. Resins may also interfere with the absorption of many other drugs. Other medications should be taken an hour before or four hours after the resins.

As with nicotinic acid, resin therapy should be begun at doses well below the anticipated maintenance dose. A dosage of 5 grams of colestipol or 4 grams of cholestyramine is begun once a day, increasing slowly to 20 to 30 grams of colestipol or 16 to 24 grams of cholestyramine per day in split doses.

Gemfibrizol is the easiest to use of the first-line medications, and it is usually well tolerated. The most common side effects are upper gastrointestinal symptoms. Abnormalities of hematologic variables and liver enzyme levels and myositis have infrequently been reported. The dosage is usually begun at 300 mg per day with the evening meal—most cholesterol is made at night—and advanced to 600 mg twice a day.

Lovastatin is also easy to use and well tolerated. Although side effects are infrequent, concerns about its long-term safety persist. Liver enzyme abnormalities and myositis with creatine kinase elevations require discontinuing the therapy in 1% to 2% of patients and should be monitored during therapy. Severe myositis and associated renal failure have been reported, usually when lovastatin has been used with other medications such as cyclosporine or gemfibrizol. Initial concerns about an increased incidence of lens opacities with the use of lovastatin have not been substantiated. The dosage of lovastatin is begun at 20 mg with the evening meal and can be increased up to 80 mg per day in split doses.

In patients in whom a single cholesterol-lowering medi-

cation has been insufficient, combinations of two or three of these medications can be used. The combined use of gemfibrizol and lovastatin, because of the greater incidence of severe myositis, should be reserved for particularly difficult patients. As with antihypertensive medications, lower doses of two agents may be preferable in preventing side effects than large doses of a single agent.

Summary

We now have sufficient evidence to recommend an aggressive program of the detection and treatment of hypercholesterolemia. All adult patients should be screened and evaluated, and treatment decisions should be based on their LDL-cholesterol levels and the presence or absence of other risk factors. Diet therapy should be initiated in motivated patients for three to six months progressing from a qualitative to a quantitative approach. Patients with persistent elevations in their LDL-cholesterol levels who accept drug therapy can be begun on a regimen of nicotinic acid, gemfibrizol or bile acid-binding resins, and, when necessary, lovastatin.

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